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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,040	06/06/2001	James Robl	P 280633 23523-0008	8078

7590 12/19/2001

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EXAMINER	
BECKERLEG, ANNE M	
ART UNIT	**PAPER NUMBER**
1632	4

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/874,040	ROBL ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-35 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As written, the claims recite "human embryonic or stem-like cells" which read on cells that are part of a human embryo which is non-statutory subject matter. See 1077 O.G. 24, April 21, 1987. The insertion of the term "isolated" before the phrase "human..." will be remedial.

Claims 18-25 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a product of nature. As written, the claims recite "Human embryonic or stem-like cells" which read on naturally occurring human embryonic or stem cells. The claims are product-by-process claims (wherein little weight is given to the process of making the product) and the product reads on a product of nature because the claims fail to recite distinguishing characteristics in the

claims. Additionally, as written, the limitation "Human embryonic or stem-like cells" reads on cells that are part of a naturally occurring human embryo which is also a product of nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for the production of human embryonic or stem-like cells comprising inserting a differentiated human cell or nucleus into an enucleated bovine oocyte under conditions suitable for the formation of a nuclear transfer (NT) unit; activating the NT units; culturing the activated NT units until greater than the 2-cell developmental stage; and culturing cells obtained from said cultured NT units to obtain human embryonic or stem-like cells. The claims are further directed to the human embryonic or stem-like cells produced by the method.

The specification discloses the preparation of nuclear transfer units via a method of nuclear transfer of adult human epithelial cell nuclei into enucleated cattle oocytes to form a nuclear transfer (NT) unit (Figure 1) by electrofusion techniques. The methods disclosed in Example 1 of the specification result in the production of 1 NT unit (16-400 cell stage) according to Table 1, page 32. Although the methods of the instant invention result in the production of 1 NT unit which applicants report propagates into what appears to be ES-like cell colonies (as determined by cell morphology); Applicants fail to demonstrate that the ES-like cells function as true ES-cells, i.e. that the cells are totipotent, or that they function as stem cells in that they are capable of differentiation into other cell-types. Applicant's specification enables the claimed method up for steps (I)-(iii); however, the specification does not enable the production of human embryonic or stem-like cells as recited in step (iv).

The unpredictability of the method as a whole lies in the need to convert a differentiated cell to a totipotent cell (embryonic stem cell). While differentiated cells may contain the same DNA complement, in differentiated tissues, not all DNA sequences are expressed. For example, a liver cell does not make rhodopsin and retinal cell structures, and retinal cells do not make clotting factors and hepatocyte structures. For a cell to go through all the steps of development, it, or its nucleus, must be reverted back to the stage where all DNA sequences can potentially be expressed, and expression regulated according to developmental stage. Applicants have not provided evidence that the cells produced by their methods are true pluripotent cells (embryonic stem cells or embryonic or stem-like cells). Applicants fail to demonstrate whether their ES-like

cells stain positive for alkaline phosphatase (AP), exhibit the formation of embryoid bodies, spontaneously differentiate into at least two different cell types, or express exclusive ES cell markers. Applicants only disclose several morphological characteristics (Example 1, page 31). Further, it is not predictable (without specific guidance) whether Applicants' ES-like cells are even cells which are capable of differentiation upon induction to a particular cellular pathway, e.g., lineage or multilineage precursor. Applicants further have acknowledged that the prior art is lacking in the production of inner cell mass cells from NT units useful to form ES cell-like colonies that could be propagated (page 6, lines 8-11). In fact, at the time of filing, the prior art has not been able to demonstrate even the isolation of naturally occurring embryonic stem cells from any mammal other than mouse. Campbell et al. teaches that, "[i]n species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species....However, as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse" (Campbell et al. (1997)Theriology, Vol. 47 (1), page 65, paragraph 2). Thus, the skilled artisan would not have found guidance from the art on the methodology of preparing embryonic stem cells or stem-like cells by nuclear transfer utilizing differentiated adult human cells or cell nuclei and bovine enucleated oocytes. For this, the artisan could **only** rely on the instant specification. Therefore, in light of the very low frequency of NT units produced by the claimed method, the lack of a showing demonstrating differentiation from the produced cells, the lack of evidence demonstrating ES cell totipotency, and the breadth of the claims, it would have required undue experimentation to practice the

invention as claimed and the skilled artisan would not have predicted success in generating embryonic stem cells or stem-like cells capable of differentiating into any type of tissue using the applicant's disclosed methodology.

In addition, the specification does not provide sufficient guidance as to methods of differentiating ES or ES-like cells into any and all tissue types. Applicants rely on prior art methods for induction of differentiation using their resulting ES-like cells. However, differentiation of ES cells is species-dependent. This observation is supported by Stice et al. (Theriogenology, 1998) who disclose that "[o]verall, an obvious conclusion of mammalian nuclear transfer studies is that the results obtained often depend on species investigated in the study." (See page 130, Species Specific Difference, 1st paragraph). Further, Stice et al. discuss that the degree of differentiation depends on the source of terminally differentiated nuclei as well as other factors (paragraph bridging pages 131-132). Thus, it is inappropriate to rely on the prior art with respect to mouse (or any other species) ES cell differentiation techniques as it applies to the ES-like cells of the instant invention. It is also not clear from the specification what contribution (functionally or structurally), if any, the bovine cytoplasm (or mitochondria) makes to the resulting ES-like cell of the instant invention. Further, in view of structural (or functional) differences in the ES-like cells of the instant invention, the skilled artisan would not reasonably expect to induce differentiation into other cell lineages using techniques in the art available for mouse ES cells. The specification fails to provide guidance and direction for parameters which

enable the claimed invention with respect to obtaining true ES or stem cells (capable of differentiation, for example).

Furthermore, the courts have stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of** any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, Applicants fail to provide guidance to the skilled artisan on any parameters which are demonstrated to be effective for the production of embryonic or stem-like cells which are capable of differentiation upon induction.

Furthermore, the specification in particular has not provided a use for human embryonic cells made by the method in that such cells, if true ES cells, have the potential upon transfer to a host to develop into a human being. As the product claims recite "Human embryonic or stem-like cells", this argument is proper in that the term "embryonic" has a well known potential in the art to give rise to a particular species of animal. It is acknowledged that Applicants contemplate the production of human stem cell multilineage precursors, however, since Applicants also discuss the ES cell potential for germ-line manipulation (pages 2-5) with respect to ES cells of

non-human species, it is not clear how and under what circumstances, humans would be so made from the ES-like cells of the invention. If Applicants do not intend for use of the cells of the invention in such a manner, Applicants may wish to choose different claim terminology better describing the cells of the invention.

In addition, the specification fails to provide sufficient guidance for the *in vivo* therapy of disease using the disclosed alleged ES or ES-like cells. The specification does not provide guidance for the parameters affecting cell delivery *in vivo* such as dosages, and routes of cell delivery that correlate with a therapeutic effect on any disease. Further, without specific guidance, it is not evident that the ES-like cells of the instant invention won't be rejected by the human patient due to the presence of mitochondria from the oocytes used for nuclear transfer (see page 11, lines 24-26). The specification also fails to provide specific guidance for generating and using ES-like cells that express an inserted gene. Without specific guidance, it is unclear whether the ES-like cells of the instant invention have the capacity to express any inserted gene, in particular any therapeutic gene. Also, the specification does not provide guidance as to the number of modified ES-like cells, the route of delivery, or the level of inserted therapeutic gene expression that would correlate with any treatment effect on any disease. As discussed above, the state of the art for producing cross-species nuclear transfer units capable of functioning as true ES cells or capable of differentiating into any particular tissue type was highly unpredictable. Further, *ex vivo* methods of gene therapy of disease were also considered highly unpredictable due to art recognized problems in the level and duration of transgene expression *in vivo* and the

targeting of cells and therapeutic genes to specific diseased tissues *in vivo*. Thus, based on the lack of guidance provided by the specification for using the disclosed ES-like cells for disease therapy, the lack of working examples demonstrating any therapeutic effect on any disease, and the unpredictable nature of *ex vivo* gene therapy methods at the time of filing, it would have required undue experimentation for the skilled artisan to treat any and all disease using the instant methodology.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of, or reasonable correlation to, producing ES-like cells capable of differentiation upon induction, the unpredictable and undeveloped art with respect to cross-species nuclear transfer (using adult differentiated nuclei) for production of ES cells capable of differentiation, in particular with respect to using differentiated, adult human cell nuclei and bovine oocytes, the unpredictable state of the art with respect to extrapolating results from ES cells of all other species to results from chimeric ES cells or human ES cells, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the claims, the phrase "human embryonic or stem-like cells" is vague and indefinite with respect to structure and function of the cells. For example, do Applicants intend to claim embryonic stem cells, stem cells, or both? Applicants refer to the term "stem cell-like" with respect to the contribution of the bovine oocyte mitochondria, however, does such a structural contribution have any effect on the function of an ES cell, such that the resulting cells can not be termed embryonic stem cells? If the contribution of bovine mitochondria has absolutely no effect on the function of the resulting ES-like cell of the invention, then how is the cell distinguished over human ES cells or human stem cells? Clarification and/or amendment to the claims is requested.

The claims also recite the phrase "inserting a desired human or mammalian cell or cell nucleus". It is unclear what types of cells or nuclei would be considered "desirable", thus the metes and bounds of the claim cannot be determined. Clarification is requested.

Further, in claim 9, the term "DMAP" should be appropriately defined, as the technical designation is not known to those of ordinary skill in the art. Amendment to the claim is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 18-25 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,716,827, 2/10/98, hereafter referred to as Tsukamoto et al..

The claims are directed to human embryonic or stem-like cells and are product-by-process claims, wherein the process of making is given little weight with respect to the product so made. It is not clear as to what the phrase "human embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. §112, second paragraph. Thus, the phrase is being interpreted as human stem cells.

Tsukamoto et al. disclose the production of human hematopoietic stem cells capable of producing members of each of the hematopoietic lineages (See Abstract and claims 1 & 2). Thus, without a distinction indicating a structural or functional difference of the claimed cells,

the human hematopoietic stem cells and differentiated cells of Tsukamoto et al. clearly meet all of the limitations of the cells of claims 18-25. Accordingly, Tsukamoto et al. clearly anticipate the claimed invention.

Claims 18-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Granerus et al. (1996) Cell Proliferation, Vol. 29, 309-314.

The claims are directed to human embryonic or stem-like cells and are product-by-process claims, wherein the process of making is not given any weight with respect to the product so made. It is not clear as to what the phrase "human embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. §112, second paragraph. Thus, the phrase is being interpreted as cells which function in a similar manner as human embryonic stem cells.

Granerus et al. disclose a human cell line, Tera 2, which functions in several aspects as a human embryonic stem cell (See Abstract). Thus, without a distinction indicating a structural or functional difference of the claimed cells, the human cells of Granerus et al. having embryonic stem cell activity meet all of the limitations of claims 18-23. Accordingly, Granerus et al. clearly anticipate the claimed invention.

Claims 18-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamane (1987) Japanese Journal of Cancer and Chemotherapy, Vol. 14, 211-219, abstract.

The claims are not clearly defined (112/2nd) or enabled (112/1), thus, the phrase "human embryonic or stem-like cells" is not distinguishable over human differentiated cells.

Yamane disclose human differentiated cells derived from epithelial cells, skin keratinocytes and endothelial cells (See Abstract). Thus, without any distinction indicating a structural or functional difference of the claimed cells, the human differentiated cells of Yamane meet all of the limitations of claims 18-25.

Accordingly, Yamane clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al. (1990) Theriogenology, Vol. 33 (1), 350 in view of Collas et al. (1994) Molecular Reproduction and Development, Vol. 38, 264-267.

The claims are directed to a method of producing human embryonic or stem-like cells via nuclear transfer of a differentiated human cell nucleus to a bovine oocyte.

Wolfe et al. teach a method of cross-species nuclear transfer using nuclei from bovine preimplantation embryos and oocytes of a varying species. Wolfe et al. disclose the production of blastocysts derived from bovine nuclei and bison ovum as well as bovine nuclei and goat ovum. Thus, the experimentation of Wolfe et al. demonstrates that mammalian nuclei may be capable of interacting with cytoplasm from other mammalian species to support normal development (See Abstract). Wolfe et al. differ from the claimed invention in that they do not propose nuclear transfer of human differentiated nuclei into bovine oocytes. However, at the time the claimed invention was made, Collas et al. disclose results indicating that transplanted differentiated nuclei may be pluripotent. Collas et al. also suggest that "a variety of differentiated mammalian cell types may promote early preimplantation development of NT embryos." (See page 266, Discussion).

In the absence of a showing of unexpected results by Applicants relating to the production of true ES cells or differentiation capacity of the ES-like cells of the invention, the cited prior art provides sufficient motivation to select cross-species differentiated mammalian cell nuclei and oocytes for use in nuclear transfer methodology with a reasonable expectation of producing at least one nuclear transfer unit of which is capable of being cultured into cells resembling ES-like cells.

Accordingly, in view of the collective cited prior art, it would have been *prima facie* obvious for one of ordinary skill in the art to select human differentiated cell nuclei and bovine

oocytes for use in nuclear transfer with a reasonable expectation of producing at least one nuclear transfer unit of which is capable of being cultured into cells resembling human ES-like cells.

Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a **reasonable** expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the group fax number is (703) 308-8724.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER